Genome-wide association study (GWAS)-identified disease risk alleles do not compromise human longevity

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Supporting Information

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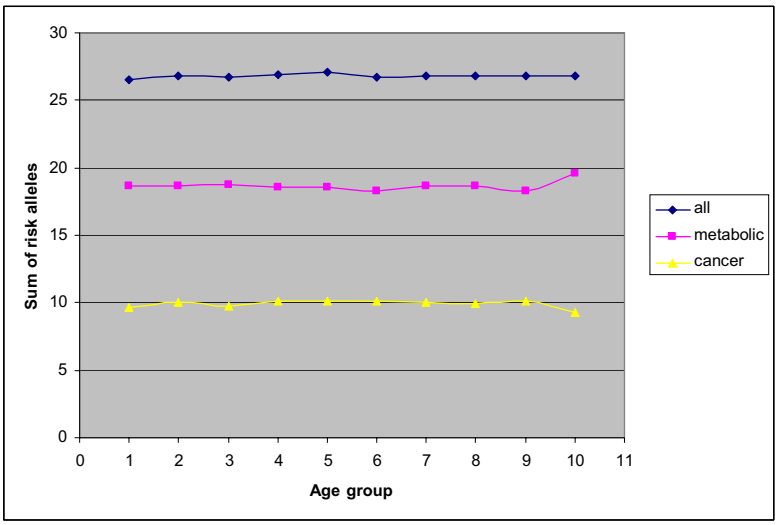

Fig. S1. The study population was divided into 10 age groups: (1) <26 y (n = 116), (2) 26–35 y (n = 576), (3) 36–45 y (n = 247), (4) 46–55 y (n = 344), (5) 56–65 y (n = 457), (6) 66–75 y (n = 135), (7) 76–85 y (n = 547), (8) 86–95 y (n = 1,029), (9) 96–98 y (n = 101), and (10) ≥99 y (n = 38). Per age group, the mean number of risk alleles was determined for the sum of all risk alleles (blue), sum of the subset of metabolic risk alleles (pink), and subset of the cancer risk alleles (yellow).

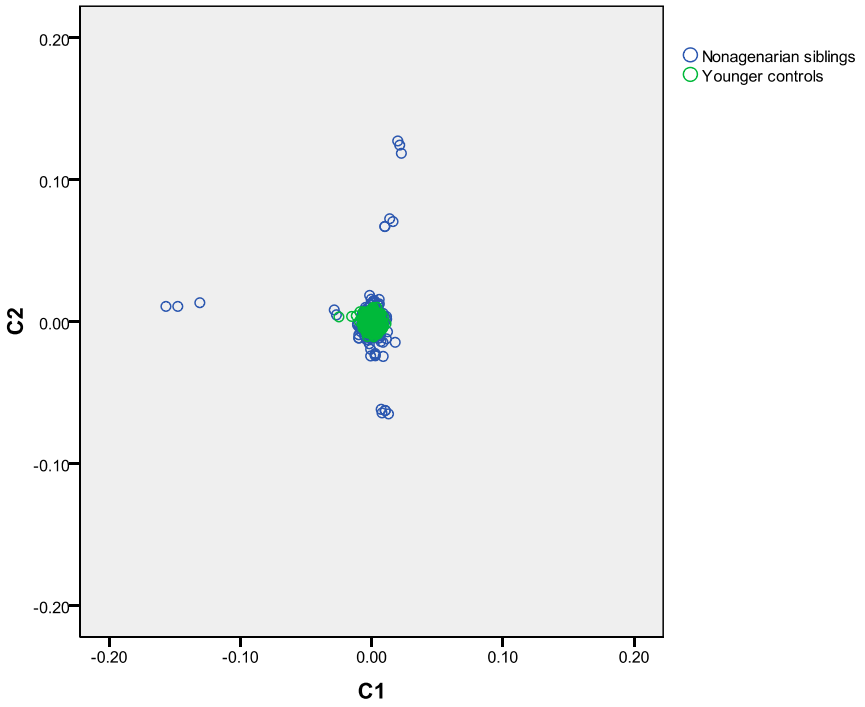

Fig. S2. Four small clusters are located apart from the main large cluster. These four clusters contain four separate families, each consisting of three nonagenarians. Because these four families report that they are of Dutch ancestry and because these are single-family clusters relatively close to the majority of the samples, we conclude that there is no substructure among the participants of the LLS to an extent that would affect our conclusions.

Table S1. Overview of loci associated with heart disease, cancer, and type 2 diabetes up to February 2009 in at least two independent GWASs

Locus	Chromosome	Nearest genes	SNP*	Position	Risk/Non risk†	Associated disease	OR§	References
1	1p13.3	CELSR2, PSRC1	rs599839	109623689	A/G	CAD	1.39	(1, 2)
			rs646776	**109620053**	**T/C**	**CAD**	—	Surrogate for rs599839 (r^2 = 0.94)
2	2q32.3	TMEFF2	**rs10497721**	**192622607**	**A/C**‡	**T2D**	—	(3)
			rs10497726	192759565	C/A‡	CAD	—	(4)
			rs10497723	192817829	G/A	T2D	2.32	(5)
3	3p25.2	PPARG	rs17036101	12252845	G/A	T2D	1.15	(6)
			rs1801282	**12368125**	**C/G**	**T2D**	1.14	(7–11)
4	3q27.2	IGF2BP2	**rs4402960**	**186994381**	**T/G**	**T2D**	1.14	(7–9, 12)
			rs1470579	187011774	C/A	T2D	1.14	(7, 13)
5	4p16.1	WFS1	**rs10010131**	**6343816**	**G/A**	**T2D**	1.15	(14, 15)
			rs6446482	6346594	G/C	T2D	1.15	(14, 15)
			rs734312	6354255	A/G	T2D	1.23/1.25¶	(14, 15)
6	5p15.33	TERT-CLPTM1L	rs402710	1373722	C/T	LC	1.18	(16)
			rs401681	1375087	G/A	LC	1.15	(17)
7	5q34	BC011998	**rs10515869**	**163444804**	**G/A**‡	**HF**	—	(4)
			rs6556756	**163821858**	**G/T**‡	**BC**	—	(18)
			rs9314033	163822784	C/A‡	BC	—	(18)
8	6p22.3	CDKAL1	rs10946398	20769013	C/A	T2D	1.12	(9, 19)
			rs7754840	**20769229**	**C/G**	**T2D**	1.12	(7, 8, 20)
			rs7756992	20787688	G/A	T2D	1.20	(12, 21)
			rs9465871	20825234	C/T	T2D	1.18/2.17¶	(10)
9	6q25.1	MTHFD1L	**rs6922269**	**151294678**	**A/G**	**CAD**	1.37	(1, 10)
10	8q24.11	SLC30A8	**rs13266634**	**118253964**	**C/T**	**T2D**	1.12	(7–9, 12, 19, 21, 22)
11	8q24.21	POU5F1,LOC727677	rs7001069	128179828	A/G‡	PC	—	(18)
			rs10505483	128194377	G/A‡	PC	—	(18)
			rs13281615	128424800	G/A	BC	1.08	(23)
			rs10505477	128476625	G/A	CC, PC	1.27/1.43	(24–26)
			rs11985829	128478414	C/T‡	CC, PC	1.08/1.22	(27)
			rs10808556	128482329	A/G	CC, PC	1.26/1.31	(26, 27)
			rs6983267	**128482487**	**G/T**	**CC, PC**	1.25/1.20	(25, 27–30)
			rs7013278	128484074	C/T‡	CC	—	(27)
			rs10505474	128486686	G/A‡	CC	—	(27)
			rs2060776	128489299	T/G‡	CC	—	(27)
			rs10956369	128492999	A/T‡	CC	—	(27)
			rs7014346	**128493974**	**A/G**	**CC**	1.19	(27, 31)
			rs4871789	128497243	A/G‡	CC	—	(27)
			rs7842552	128500876	G/A	CC	1.15	(31)
			rs1447295	**128554220**	**A/C**	**PC**	1.43/2.23¶	(26, 28, 32, 33)
			rs4242382	128586755	**A/G**	**PC**	1.66/2.22¶	(29)
			rs7837688	128608542	T/G	**PC**	1.46/2.03	(28)
12	9p21.3	CDKN2BAS	**rs564398**	**22019547**	**T/C**	**T2D, CAD**	1.12/1.21¶	(9, 34)
			rs10757274	22086055	G/A	CAD	1.18/1.29¶	(35)
			rs1537371	22089568	A/C‡	CVD	—	(4)
			rs1556516	22090176	C/G‡	CVD	—	(4)
			rs10511701	22102599	C/T‡	CVD	—	(4)
			rs2383206	22105026	G/A	CAD	1.26/1.26¶	(35)
			rs2383207	22105959	G/A	CAD	1.25	(36)
			rs10757278	**22114477**	**G/A**	**CAD**	1.28	(11, 36)
			rs1333049	**22115503**	**C/G**	**CAD**	1.47/1.90¶	(1, 10)
			rs10811661	**22124094**	**T/C**	**T2D**	1.20	(7–9, 11, 12, 19)
13	10q23.33	HHEX	**rs1111875**	**94452862**	**C/T**	**T2D**	1.13	(7–9, 12, 22)
			rs5015480	94455539	C/T	T2D	1.13	(9)
			rs7923837	94471897	A/G	T2D	1.22/1.45¶	(12, 22)
14	10q25.2	TCF7L2	rs7901695	114744078	C/T	T2D	1.37	(9, 37)
			rs4506565	114746031	T/A	T2D	1.36/1.88¶	(10)
			rs7903146	**114748339**	**T/C**	**T2D, CC**	1.37/1.25–2.15¶	(7, 10, 19, 22, 37–40)
			rs12255372	114798892	T/G	T2D, BC, PC	1.64/1.21–1.37¶/1.09–1.15¶	(37–39, 41, 42)
15	10q26.13	FGFR2	rs1219648	123336180	G/A	BC	1.32	(43, 44)
			rs2420946	**123341314**	**T/C**	**BC**	1.32	(43, 45)
			rs2981582	123342307	A/G	BC	1.26	(23, 45)

Table S1. Cont.

Locus	Chromosome	Nearest genes	SNP*	Position	Risk/Non risk†	Associated disease	OR§	References
16	11p15.1	KCNJ11	rs5215	17365206	C/T	T2D	1.14	(9)
			rs5219	**17366148**	**T/C**	**T2D**	1.14	(7, 8, 12, 19)
17	12q21.1	TSPAN8	**rs1495377**	**69863368**	**G/C**	**T2D**	1.28/1.51¶	(10)
			rs7961581	69949369	C/T	T2D	1.09	(6)
18	15q25.1	LOC123688, CHRNA3	**rs8034191**	**76593078**	**T/C**	**LC**	1.30	(46–48)
			rs1051730	76681394	G/A	LC	1.31	(16, 46, 47, 49)
			rs8042374	76695087	G/A‡	LC	—	(17)
19	16q12.1	TOX3	**rs8051542**	**51091668**	**T/C**	**BC**	1.09	(23)
			rs12443621	**51105538**	**G/A**	**BC**	1.11	(23)
			rs3803662	51143842	T/C	BC	1.20	(23, 50, 51)
20	16q12.2	FTO	**rs8050136**	**52373776**	**A/C**	**T2D**	1.17	(8, 9, 19, 52)
			rs9939609	52378028	A/T	T2D	1.34/1.55¶	(10, 52)
21	17q12	HNF1B	**rs757210**	**33170628**	**T/C**	**T2D**	1.12	(53, 54)
			rs4430796	**33172153**	**A/G**	**PC, T2D**	1.22/0.91¶	(29, 54)
			rs7501939	33175269	C/T	PC	1.19	(54, 55)
			rs3760511	33180426	C/A	PC	1.16	(54)
22	18q21.1	SMAD7	**rs4939827**	**44707461**	**T/C**	**CC**	1.18	(30, 31, 56)
			rs12953717	44707927	T/C	CC	1.17	(31, 56)
			rs4464148	44713030	C/T	CC	1.15	(56)
23	Xp11.22	NUDT11	**rs5945572**	**51246423**	**A/G**	**PC**	1.23	(57)
			rs5945619	51258412	T/C	PC	1.19	(58)

BC, breast cancer; CAD, coronary artery disease; CC, colon carcinoma; CVD, cardiovascular disease; HF, heart failure; LC, lung cancer; PC, prostate cancer; T2D, type 2 diabetes.

*SNPs genotyped in the LLS are denoted in bold.

†Major allele of genotyped SNPs is underlined.

‡Risk allele is not found in the literature; data are retrieved from SnpPer (ChiP Bioinformatics), and the minor allele is denoted first.

§OR per allele.

¶OR in heterozygotes and homozygotes, respectively.

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Table S2. Cross-tabulation of 10% lower and upper tails of the risk allele distribution in the control and long-lived groups

	All risk alleles	
	<23 alleles (9.4%)	≥31 alleles (12.9%)
Control	172 (9.1%)	237 (12.6%)
Long-lived	166 (9.8%)	225 (13.2%)

OR = 0.99; 95% CI: 0.97–1.03; $P = 0.909$.

Table S3. Cross-tabulation of 10% lower and upper tails of the metabolic risk allele distribution in the control and long-lived groups

	Metabolic risk alleles	
	<15 alleles (6.8%)	≥23 alleles (8.5%)
Control	136 (7.2%)	176 (9.3%)
Long-lived	108 (6.3%)	129 (7.6%)

OR = 0.99; 95% CI: 0.95–1.03; $P = 0.644$.

Table S4. Cross-tabulation of 10% lower and upper tails of the cancer risk allele distribution in the control and long-lived groups

	Cancer risk alleles	
	≤7 alleles (11.9%)	≥13 alleles (12%)
Control	220 (11.7%)	244 (12.9%)
Long-lived	208 (12.2%)	188 (11.0%)

OR = 0.97; 95% CI: 0.92–1.01; $P = 0.135$.

Table S5. Association of GWA-identified disease risk alleles with longevity

					Risk allele frequency				Meta-analysis		
Chromosome	SNP	Position	Disease profile*	Risk/ Nonrisk[‡]	LLS controls	LLS 90+ subjects	NTR controls	Leiden 85 Plus Study subjects	OR[§]	95% CI[§]	*P* value[¶]
1p13.3	rs646776	109620053	M	**T**/C	0.786	0.737	0.778	0.777	0.88	0.79–0.99	0.035
2q32.3	rs10497721	192622607	M	A/**C**	0.092	0.113	0.093	0.090	1.07	0.91–1.26	0.367
3p25.2	rs1801282	12368125	M	**C**/G	0.884	0.883	0.892	0.873	0.89	0.76–1.03	0.131
3q27.2	rs4402960	186994381	M	T/**G**	0.316	0.284	0.300	0.305	0.96	0.86–1.06	0.374
4p16.1	rs10010131	6343816	M	**G**/A	0.586	0.562	0.590	0.600	0.98	0.89–1.08	0.742
5q34	rs10515869	163444804	—	A/G	0.444	0.424	0.440	0.434	0.95	0.87–1.05	0.320
5q34	rs6556756	163821858	—	T/G	0.089	0.112	0.116	0.096	0.97	0.83–1.13	0.722
6p22.3	rs7754840	20769229	M	C/**G**	0.324	0.332	0.306	0.317	1.05	0.95–1.17	0.391
6q25.1	rs6922269	151294678	M	A/**G**	0.255	0.307	0.247	0.250	1.12	1.00–1.25	0.033
8q24.11	rs13266634	118253964	M	**C**/T	0.686	0.693	0.696	0.701	1.03	0.93–1.15	0.597
8q24.21	rs6983267	128482487	C	**G**/T	0.528	0.526	0.525	0.516	0.98	0.87–1.08	0.606
8q24.21	rs7014346	128493974	C	A/**G**	0.386	0.376	0.369	0.352	0.95	0.86–1.05	0.227
8q24.21	rs1447295	128554220	C	A/**C**	0.142	0.110	0.116	0.122	0.91	0.79–1.06	0.235
9p21.3	rs564398	22019547	M	**T**/C	0.572	0.559	0.596	0.563	0.90	0.82–1.00	0.037
9p21.3	rs10757278	22114477	M	G/**A**	0.457	0.461	0.476	0.428	0.90	0.81–0.99	0.026
9p21.3	rs1333049	22115503	M	**C**/G	0.542	0.543	0.527	0.570	1.11	1.00–1.22	0.030
9p21.3	rs10811661	22124094	M	**T**/C	0.823	0.808	0.796	0.826	1.08	0.96–1.23	0.216
10q23.33	rs1111875	94452862	M	**C**/T	0.593	0.594	0.598	0.605	1.02	0.93–1.13	0.680
10q25.2	rs7903146	114748339	M	T/**C**	0.278	0.275	0.264	0.273	1.02	0.92–1.14	0.720
10q26.13	rs2420946	123341314	C	T/**C**	0.392	0.359	0.396	0.391	0.93	0.84–1.103	0.167
11p15.1	rs5219	17366148	M	T/**C**	0.378	0.344	0.370	0.359	0.91	0.83–1.01	0.080
12q21.1	rs1495377	69863368	M	**G**/C	0.505	0.528	0.494	0.519	1.10	1.00–1.22	0.046
15q25.1	rs8034191	76593078	C	**T**/C	0.682	0.682	0.662	0.683	1.06	0.95–1.18	0.270
16q12.1	rs8051542	51091668	C	**T**/C	0.730	0.730	0.756	0.715	0.88	0.79–0.98	0.023
16q12.1	rs12443621	51105538	C	G/**A**	0.425	0.439	0.421	0.446	1.09	0.99–1.20	0.083
16q12.2	rs8050136	52373776	M	A/**C**	0.383	0.371	0.391	0.388	0.97	0.88–1.08	0.599
17q12	rs757210	33170628	M, C	T/**C**	0.384	0.381	0.387	0.384	0.99	0.90–1.09	0.772
17q12	rs4430796	33172153	M, C[†]	**A**/G	0.486	0.501	0.484	0.494	1.05	0.96–1.16	0.320
18q21.1	rs4939827	44707461	C	**T**/C	0.494	0.528	0.491	0.494	1.06	0.97–1.17	0.202
Xp11.22	rs5945572	51246423	C	A/**G**	0.354	0.375	0.341	0.366	0.99	0.91–1.08	0.852

*M indicates that the risk allele contributes to metabolic disease (coronary artery disease or type 2 diabetes); C indicates that the risk allele contributes to cancer.

[†]Major allele (A) has been associated with risk for cancer, whereas the minor allele (G) has been associated with type 2 diabetes.

[‡]Major allele is indicated in bold.

[§]Estimation of OR and 95% CI was performed with robust SEs to take into account family dependency in the LLS.

[¶]*P* values were calculated using robust SEs to take into account family dependency in the LLS.

Table S6. Sum of risk alleles per age group

			Mean sum of risk alleles (SE)					
Age group	Age range	*N*	All		Metabolic		Cancer	
1	<26 y	116	26.56	(0.30)	18.68	(0.27)	9.70	(0.23)
2	26–35 y	576	26.80	(0.14)	18.62	(0.12)	10.01	(0.09)
3	36–45 y	247	26.72	(0.21)	18.71	(0.18)	9.79	(0.13)
4	46–55 y	344	26.92	(0.17)	18.58	(0.14)	10.08	(0.12)
5	56–65 y	457	27.11	(0.16)	18.60	(0.14)	10.09	(0.10)
6	66–75 y	135	26.75	(0.30)	18.25	(0.24)	10.17	(0.19)
7	76–85 y	547	26.83	(0.14)	18.63	(0.12)	10.01	(0.09)
8	86–95 y	1,029	26.78	(0.10)	18.61	(0.09)	9.92	(0.07)
9	96–98 y	101	26.82	(0.31)	18.25	(0.28)	10.11	(0.20)
10	≥99 y	38	26.84	(0.47)	19.61	(0.45)	9.29	(0.32)

Other Supporting Information Files

Dataset S1 (XLS)